Studies from the Institute of Pathology

CASE IX.

A PATIENT WITH MELANOMA. A.2811.

Clinical History.

The patient was a man of 59 years. His previous history gave no facts of importance. He was admitted to hospital suffering from weakness in the left arm and left leg, which he had first noticed about five weeks previously. This weakness was of gradual onset. During the past two weeks he vomited occasionally, this vomiting showing no relationship to food.

Whilst in hospital several pigmented spots were noted on the front of his chest and also on his back. These appeared to be beneath the skin, and in spite of careful search, no nævus could be discovered. In view of this, and because of his cerebral symptoms, examination of his ocular fundi was carefully carried out. A small tumour was discovered in the left eye.

Post-Mortem (J. McM.).

The body is that of a poorly nourished elderly male subject. It shows normal male distribution of body hair and subcutaneous fat. There is no jaundice and no œdema. Eyes, ears, and nose appear healthy. Rigor mortis is present. Numerous small spherical nodules are present beneath the skin of the chest and anterior abdominal wall. These are purplish-black in colour, and vary in size from 1 to 10 mm. in diameter.

Body Cavities.—The peritoneal cavity contains no free fluid. There are numerous small pigmented nodules in the tissues. Both pleural sacs are partly obliterated by dense fibrous adhesions and contain three ounces of greenish-yellow fluid. The pericardial sac contains four ounces of discoloured fluid, and its surfaces are studded with black nodules of varying size.

Heart.—The heart is normal in size and shape. Its surface is covered by numerous greyish-black nodules. Some of these extend up to the aorta. The right auricle is dilated. Its endocardium appears injected, and shows numerous tumour-nodules. The tricuspid valve is thin and slightly dilated. There is extensive replacement of the myocardium of the ventricle by black masses of tumour-tissue. The pulmonary valves and artery appear normal. The left auricle is less extensively involved than the right. The mitral valve is normal. The muscle of the ventricle is pale in colour and is heavily infiltrated by masses of tumour. Some of these nodules appear as small pedunculated nodules on the endocardium, and on the surface of these are small fibrinous thrombi. The aortic valve is normal.

Lungs.—The pleura over the right lung shows dense fibrous adhesions. Numerous rather flattened tumour-nodules are present just beneath the pleura. The glands at the hilum are slightly enlarged, and on section are seen to be replaced by tumour-tissue. The bronchi show nothing of note. On section, the lung tissue appears

œdematous, with numerous small reddish-black tumour-nodules scattered throughout.

The left lung presents a similar appearance, but the deposits of tumour-tissue, more especially in the lower lobe, are larger and more numerous.

Liver.—This is normal in size. Its capsule is smooth. The common bile-duct is patent. The gall-bladder is thin-walled and contains no stones. On section there are numerous nodules of tumour-tissue. The majority of these are greyish-black in colour, but others appear white. The liver lobules are relatively distinct. The radicles of the portal vein and bile-ducts appear normal.

Spleen.—This weighs eight ounces. Its capsule is raised to cover many rather rounded masses, some of which measure 2 cm. in diameter. On section, the malpighian corpuscles are distinct. The pulp is red, but is replaced in part by numerous nodules of tumour-tissue, the great majority of which are deeply pigmented.

Pancreas.—This is normal in size. Its ducts are patent. The acinar tissue appears normal, but scattered through it are numerous small pigmented nodules 1 to 3 mm. in diameter.

Stomach and Intestines. — The mucosa of the stomach is studded over with sessile, flat, greyish-black nodules, many of which show ulceration. Similar nodules are seen in the first part of the duodenum. Tumour-nodules are also found in the mucosa of the small intestine and appendix. No tumour is seen in the cæcum, ascending or transverse colon, but beginning in the region of the splenic flexure the nodules reappear, and in the descending colon many of these project into the lumen as small pigmented polypi. The rectum and anal canal show no lesions.

Kidneys.—Pigmented tumour tissue is present in the perinephric fat. The capsule is easily removed, leaving a smooth surface on which many small black nodules project. On section, several small areas of cortical infarction are present in addition to the masses of tumour. The renal tissue otherwise appears normal. The pelves and ureters are healthy.

Bladder.—The bladder is thick-walled. Its mucosa is congested, and shows several polypoid masses of tumour. Pigmented nodules are also seen in the prostate and perivesicular tissues.

Adrenals.—These are much enlarged, measuring 2 to 5 cm. in thickness. On section, they appear almost entirely replaced by brownish-black tumour-tissue. A few small islands of yellowish cortical tissue can be distinguished in the periphery of the tumour mass. These glands contain the largest deposit of the tumour.

Neck Organs.—The tongue shows deposits of tumour towards its base. There is no ulceration. The pharynx and fauces are congested and show similar nodules. Tumour-tissue is present in the tracheal mucosa, thyroid cartilage, and thyroid gland. The œsophagus appears healthy, but pigmented nodules are present in the lower half.

Brain.—The dura is firmly adherent to the skull, and shows on its meningeal surface several tumour-nodules about 1 cm. in diameter. The leptomeninges are

thin, but show pigmentation over the pre-central gyrus on the median aspect of the right hemisphere. There is some flattening of the convolutions. On section, the right pre-central gyrus is partly replaced by a nodule of tumour-tissue 1.5 cm. in greatest diameter. Around this and extending to a depth of 3 cm. into the adjacent white matter is an area of recent hæmorrhage. Small nodules of tumour-tissue, 1 to 3 mm. in diameter, are also seen scattered in various parts of the cortex. The mid-brain and cerebellum show no lesion.

Hypophysis.—This is increased in size. On its anterior lobe is a rounded pigmented nodule, 3 mm. in diameter. On section, this is seen to extend deeply into the glandular tissue.

Eyes.—The periorbital tissues show many small pigmented areas. The left eye shows three small tumour-nodules in the retina adjacent to the head of the optic nerve.

Microscopical Examination.

Heart.—The myocardium is extensively infiltrated by masses of tumour-cells. These cells are polygonal or cubical in shape, and appear epithelial in character. There is a marked tendency for the development of an alveolar arrangement of the neoplastic cells, and in some areas this simulates acinar formation, but more careful examination shows that the apparent glands are formed by the central breakdown of cells. Mitotic figures are not uncommon. Many of the cells contain granules of a brown pigment. This pigment does not give the prussian-blue reaction, does not stain with any fat-stain, but darkens with silver nitrate (five per cent. solution at 37°C.). These are the commonly accepted histological reactions of the melanin group of pigments. Tumour-cells can be seen invading the walls of tributaries of the coronary veins.

Lungs.—Many alveoli are filled with œdema fluid. There are numerous nodules of pigmented tumour-cells, one of which is seen growing as a polypoid mass into the lumen of a medium-sized bronchus. Free tumour-cells are found in many of the alveoli. The peribronchial lymphatics are distended with new growth.

Liver.—The tumour-nodules show the pseudo-acinar structure well developed. Some nodules show fine intra-cellular pigment, whilst others show no evidence of pigment formation. Many Kupffer cells are distended with pigment granules. The liver-cells show no abnormality.

Spleen.—The tumour-nodules have a similar structure to those already described. In addition to the gross nodules, numerous small groups of neoplastic cells are found in distended sinusoids, and the sinusoidal cells contain melanin pigment.

Adrenals.—It is difficult to find any adrenal tissue. The tumour-cells are very deeply pigmented, and are arranged in a pattern very similar to that of the normal adrenal. In the deeper parts of the tumour the pseudo-glandular structure reappears. No medulla is seen.

Kidneys.—Secondary deposits are seen in the cortex. Many glomeruli also show tumour emboli composed of clumps of two or more cells, very often only recognised as neoplastic cells by reason of their pigment content. Small deposits are present in the peri-pelvic fat.

Thyroid.—The tumour-nodules here tend to be composed of sheets of polygonal cells with a variable melanin content. The tumour-cells tend to invade the thyroid acini, and in the earliest stages of invasion grow around the acinus on the basement membranes. The thyroid tissue is in no way abnormal.

Brain.—The tumour-tissue shows a curious tendency to perivascular growth resulting in a papilliform structure. In the perivascular spaces, phagocytic cells containing pigment derived from the breakdown of tumour-cells are seen. The hæmorrhagic area is surrounded by proliferating astrocytes. Numerous small capillary tumour emboli are found in the cortex, and in some areas the tumour-cells are present in the sub-arachnoid space.

Hypophysis.—The anterior lobe contains a metastasis occupying about one-fourth of its volume. It is deeply pigmented, and has grown into the colloid-filled spaces of the pars intermedia. A small deposit is also present in the pars nervosa.

Anatomical Diagnosis.

Melanoma of unknown origin: ? adrenal: metastatic deposits in liver, spleen, heart, lungs, skin, brain, thyroid, hypophysis, kidneys, pancreas, and intestines: Infarcts in kidney: Cerebral hæmorrhage: Terminal œdema of lungs.

Comment.

From the clinical side this patient presented the appearance of a cerebral lesion resembling in some ways that of a "stroke" due to cerebral thrombosis. However, the history of gradual onset of the left-sided weakness was not suggestive of a cerebral vascular accident, and the more careful examination of the patient revealed the pigmented nodules in the skin and the lesions in the eye. Once these had been noted, the probability was that the nervous symptoms were due to a deposit of tumour-tissue in the path of the motor neurones supplying the left side of the body. From the position of the lesion found at autopsy, it is probable that the weakness of the left leg preceded all other motor symptoms, and that much of the paralysis noted was due to the subsequent development of an intra-neoplastic hæmorrhage.

From the pathological viewpoint this is an interesting case in several ways. Firstly, it is a good example of an extensive dissemination of tumour-cells by the blood-stream. The result of this dissemination is rendered more striking by reason of the pigmentation of the deposits, but in its essential characters a similar process is often seen in many other non-pigmented neoplasms. The evidence in favour of blood dissemination is marked. Thus we have tumour-cells in the coronary veins of the heart, tumour emboli in the renal glomeruli, and pigment phagocytosed by the reticulo-endothelial cells in the liver and spleen. Like most other examples of tumour-spread, evidence for other modes of extension is not wanting. Thus in the lungs there is direct invasion of bronchi and spread by the air passages to the alveoli. The invasion and replacement of the hilum lymph-nodes indicate a lymphatic spread from the nodules in the pulmonary tissue, whilst, finally, there is microscopical evidence of the spread of neoplastic cells by the cerebro-spinal fluid. It is thus obvious that this tumour has utilised practically every preformed pathway in its spread throughout the organs of the body.

The second point of interest arises from the difficulty in establishing the origin

of the tumour. Clinically the primary tumour has produced no symptoms, and the clinical history is merely a résumé of those symptoms resulting from the destruction of a specialised portion of the cerebral nervous system. A breast carcinoma with similar latency of symptoms and signs of the primary tumour has already been studied in this series (Case III). Pathologically, the distribution of the tumour is so extensive that it would be difficult to defend any particular site as its origin. Pigmented tumours usually arise in one of two sites—(1) from pigmented moles in the skin, and (2) from the choroid of the eye. Much more rarely, pigmented tumour may arise in the meninges, and a few examples, by no means generally accepted, have been thought to originate in the adrenals. Pigmented tumours form also in the epidermis, but these differ in structure from those arising in moles.

The most common type of melanoma is that which arises from a congenital mole. Histologically, such moles are seen to consist of peculiar abnormal cells situated in the dermis. These cells have the property of being able to produce the pigment melanin, but whilst it is agreed that they form the starting-point of the neoplastic process, their nature is a matter of much debate. Dawson (1925) derives the nævus cells from the pigment-producing basal layer of the epidermis, and maintains that all forms of melanomata, including those arising from the choroid, are of epithelial origin. Bloch, using dioxyphenylalanin, developed a staining reaction which was positive in those cells capable of producing melanin.

The frequent association of moles with von Recklinhansen's neurofibromatosis led Soldan (1899) and, more recently, Masson (1921, 1926) to re-investigate their origin, and the latter author has produced strong evidence that these malformations are in some way related to the end-apparatus of sensory nerves.

Comparative pathology has only served to make the problem more obscure, as in the lower animals the function of pigment production appears to reside in a specific mesoblastic cell—the chromatophore. In the human, however, the role played by the chromatophore in the origin of the melanoma is by no means clear.

The actual structure of the group of melanomata gives little help in arriving at any opinion as to the true nature of their cells of origin. Apart from the production of pigment, they present very variable histological appearances, at one time simulating sarcomata, at another carcinomata. Indeed, sections from various parts of the same tumour may present appearances completely unlike. Even Bloch's "dopa" reaction is not always of use. It is not positive in tumours of choroidal origin. Indeed, it would appear that it is a mistake to assume that all pigmented tumours arise from a common cell type, and that the group of tumours known as melanomata may include tumours of diverse origin having, however, the common function of pigment production.

In the present case the histological picture is highly suggestive of a carcinoma —a melano-carcinoma. In spite, however, of very careful search, no skin lesion which could be considered the primary source was found. The skin lesions were subcutaneous and did not present the histological structure of a nævus. The eyes too were excluded as the origin. Thus, by virtue of negative incidence, we are forced to consider the possibility of a visceral site for the primary tumour, and

here the most likely organ is the adrenal. Benign melanotic tumours are rarely seen in this organ, but we have seen one, and Luksch has also described their occurrence. The one studied by ourselves was cortical in position and bore no resemblance to medullary tissue. The present case resembles others reported, in that the lesion is bilateral. This fact renders us dubious of the adrenal origin of these tumours, though the occurrence of benign pigmented adrenal tumours convinces us of the possibility of such an origin. Apart from a possible adrenal origin, the study of the morbid anatomical findings precludes the establishment of any other viscus as the primary site of the tumour.

In summary, therefore, a case of widely disseminated melanoma is reported. The common sites of origin of this type of tumour, skin and eye, were eliminated. The evidence suggests an adrenal origin, but the bilateral affection of the adrenal renders this doubtful. The case, however, constitutes an excellent example of blood-spread, air-spread, and lymphatic-spread of a neoplasm.

REVIEWS

CLINICAL PRACTICE IN INFECTIOUS DISEASES. By E. H. R. Harries, M.D., M.R.C.P., D.P.H., and M. Mitman, M.D., M.R.C.P., D.P.H., D.M.R.E. With a foreword by W. Allen Daley, M.D., F.R.C.P., D.P.H. 1940. Edinburgh: E. & S. Livingstone. Pp. 468. 17s. 6d. net.

THIS text-book contains 468 pages, divided into thirty-seven chapters, of which the first eleven, comprising ninety pages, are devoted to general principles, e.g., notification, modes of infection, clinical methods of diagnosis with descriptions of rashes, laboratory aids, control and management of and diet in infectious diseases. Although this method of approach obviates a good deal of repetition, it is open to question whether it is the most suitable method for students beginning the subject. Without doubt it has much to commend it in the case of more advanced students, such as hospital residents, D.P.H. students, general practitioners, or even medical officers of health and specialists in fevers.

The authors have included diseases which they consider likely to assume increasing importance under war conditions, e.g., tetanus, typhus, relapsing fever, infection by leptospira icterohæmorrhagiæ (Weil's disease). The last-named has assumed increased importance in the United Kingdom in civilian life during the past few years, and is now listed as an industrial disease under the Workmen's Compensation Act.

On page 38 we read: "Because it is not uncommon in *typhoid fever,* the syndrome associated with a severe toxæmia has been called the *typhoid state.*" This is scarcely correct; surely in this expression the word *typhoid* is used in its literal sense, namely, *"like typhus."* On page 300, in dealing with the differential diagnosis of cerebro-spinal fever, it is stated that in typhus the Wilson-Weil-Felix reaction is positive, but it is not pointed out that it is unlikely to be positive before the end of the first week. In the routine treatment of rubella we may well question the value of a saline purge. Latin inflexions are not always treated seriously; for example, we find morbill*us* bullosi, flagell*æ,* etc.

In spite of these minor criticisms, this book may be warmly recommended, especially to those already in the profession, as a most readable, up-to-date, and sufficiently detailed account of "Clinical Practice in Infectious Diseases." The authors are to be congratulated on such an achievement, and the publishers on the attractive way in which the volume has been produced—and at such a moderate price.

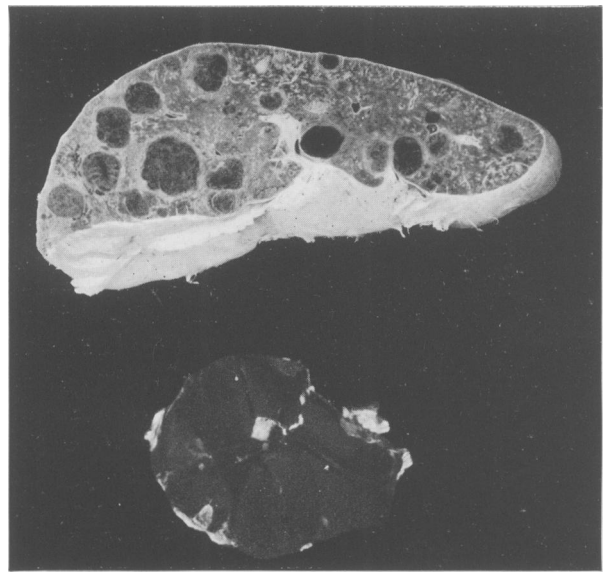

Fig. 1.
To show the number and size of the metastatic deposits in the spleen. The lower organ is the left adrenal, which is almost completely replaced.

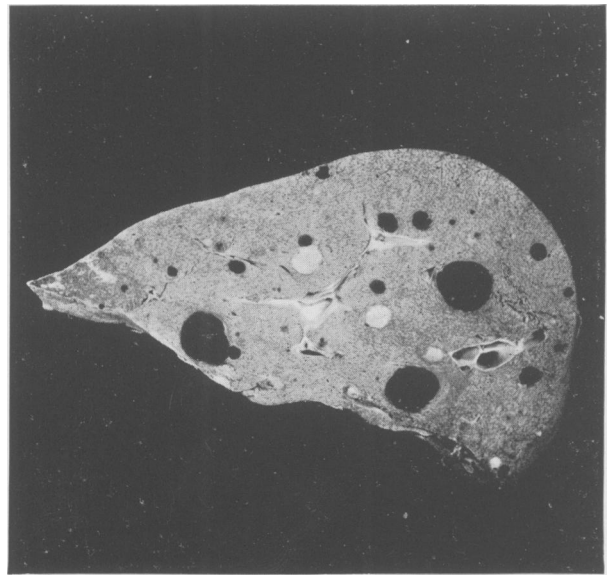

Fig. 2.
To illustrate the involvement of the liver, and the development of both pigmented and non-pigmented nodules.

Photographs by Mr. D. McA. Mehaffey.

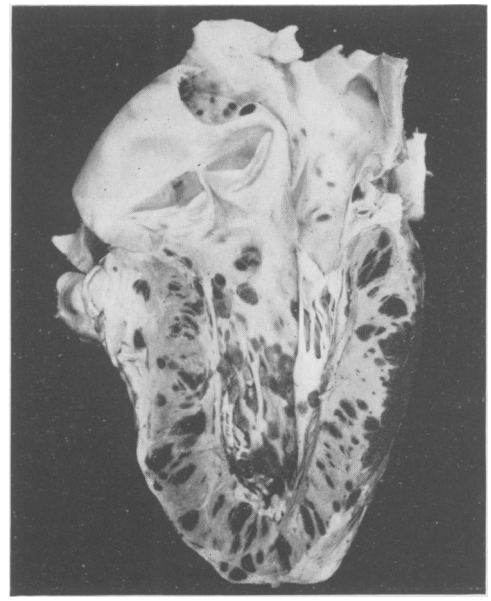

Fig. 3.
To show the extensive cardiac involvement. Note the absence of any clinical signs of these lesions.

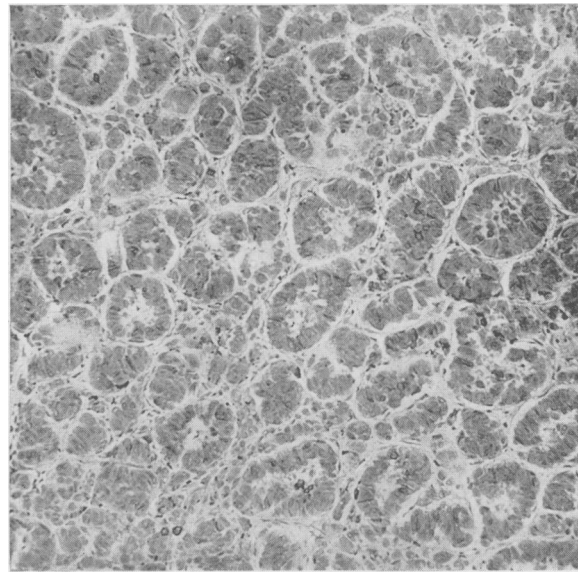

Fig. 4.
A pigmented deposit in the liver showing the epithelial characters of the neoplasm, and its marked tendency to produce pseudo-glandular structures.

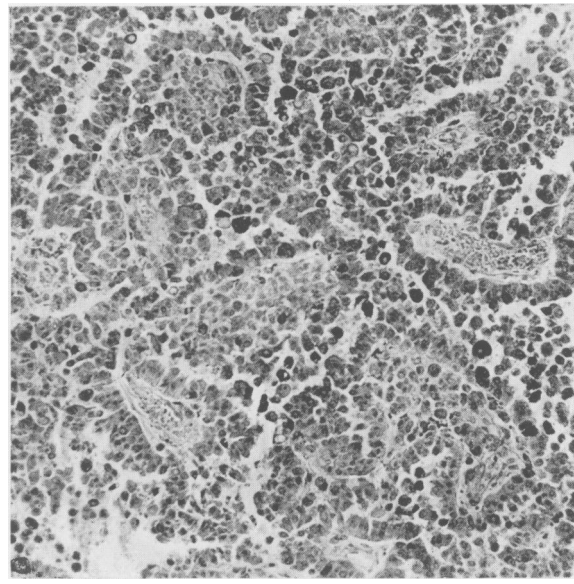

Fig. 5.

The cerebral metastasis, showing the perivascular arrangement of pigmented epithelial cells.

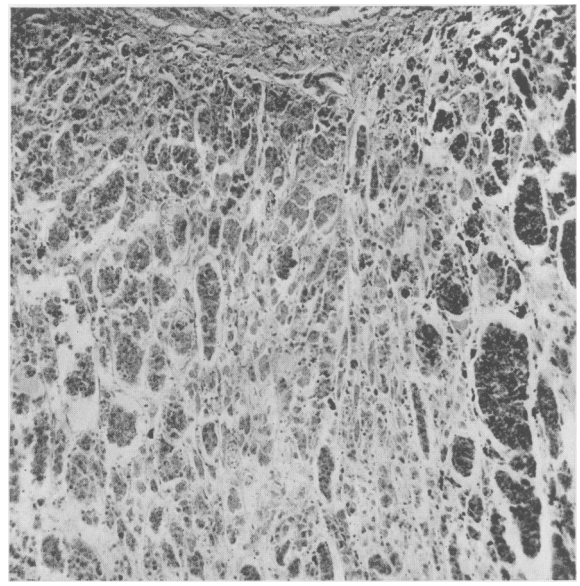

Fig. 6.

A section of the adrenal gland. A pigmented portion of the tumour is seen to the right. The tissue on the left is non-pigmented tumour, and only a few cells of the adrenal cortex survive in the centre of the field.